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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/813,156	03/31/2004	Jagmohan Singh	Q80880	4448

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SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, DC 20037

EXAMINER	
MARVICH, MARIA	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/813,156	SINGH ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-62* is/are pending in the application.

4a) Of the above claim(s) *25-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-24 as drawn to SEQ ID NO:1) in the reply filed on 5/23/07 is acknowledged. Applicants' reply is persuasive and as such the restriction between Groups I and II as well as between III and IV have been withdrawn. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement between I-II and III-IV, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

Claims 25-62 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5/23/07.

Specification

The title of the invention, *Novel temperature regulated promoters and expression vectors for proteins from Schizosaccharomyces pombe*, is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The use of novel in the title is objected to as inventions before the US Patent and Trademark Office are presumed to be novel.

Claim Objections-minor informalities

Claims 1-24 are objected to because of the following informalities: the claims require an article at the start of each claim. It is customary to begin a claim using the articles --A-- or --An-- in independent claims and when referring to previous claims i.e. "Promoters as claimed in claim1" it is customary to use --The--. In the instant claims it would be remedial to recite in the dependent claims, --The promoter (vector) as recited in claim--.

Claims 3-6, 9, 15-18 and 21 describe expression capabilities of GFP, β-galactosidase and *cdc-18* by the instant promoters. However, the promoter as recited does not include explicitly recite operable linkage to the recited genes. It would be remedial to indicate in the claims that the promoter is operably linked to one of GFP, β-galactosidase or *cdc-18.*

Claims 12 and 24 recite that the promoters reduce the level of proteolytic degradation, which requires that the promoter be expressed in a cell. While it is clear that proteolytic degradation requires that the promoter be present in the cell, the claims do not provide these limitations in the claims. It would be remedial to indicate that the promoter is in a cell.

Claim 13 recites vectors having Accession No. It would be remedial to recite that the vector -- is deposited under Accession number --. Secondly, in subsections (a) and (b), "expression vector" requires an article. It is customary when referring to limitations previously recited to use the article --the-- or --said--. As well, the inclusion of the promoter in the vector would be better described as --comprising-- as opposed to "is harbouring".

Claim 14 recites "the said" whereas it is not necessary to use both terms "the" and "said" as these terms are redundantly used in the instant claim. It would be remedial to delete with "the" or "said".

Appropriate correction is required.

Claim Objections-under 37 CFR 1.75(c)

Claims 14-24 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. As an initial issue, the vectors do not comprise components required of the vectors of claims 15-21. Specifically, the deposited vectors do not have the capability of expression of GFP, β-galactosidase and *cdc-18* because they are not present in the vectors. As well, in claims 14, 16, 20 and 22-24, the claims describe functional limitations that are inherently present in either pRJK2 (claim 14, 16, 20, 22-24) or pRKJ3 (claim 14 and 22-24). Because there are no additional structural requirements of the vector based upon the functional properties, the claims do not further limit claim 13.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1 and 7-13 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims, as written, do not sufficiently distinguish over cells that exist naturally because the claims do not particularly point out any non-naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206, USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor., e.g. by insertion of "Isolated" or "Purified"

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12, 15, 16 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in that the metes and bounds of "promoter having SEQ ID No. 1, designated as *nmt-185* and SEQ ID No, 2, designated as *nmt-146*" are unclear. It is unclear if the promoter must have both sequences or one or the other. It appears from the recitations in the dependent claims that two promoters are being claimed, one comprising SEQ ID NO:1 and one comprising SEQ ID NO:2. If so, it would be remedial to recite --promoter selected from the group consisting of --. The dependent claims would need to be amended accordingly to recite --promoter-- as opposed to "promoters". If it is a single fusion promoter, it would be remedial to amend the dependent claims to --promoter-- as opposed to "promoters". Secondly, as in claim

nmt-185 and *nmt-146.* If it is the SEQ ID No: then it would be remedial to recite for example, --SEQ ID NO:1, *nmt-185*--.

Claims 3, 4, 15 and 16 are vague and indefinite in that the metes and bounds of "expression of said promoter is about 95% (91.4%) within 3 hrs" are unclear. It is unclear to what expression is compared such that the level is 95% or 91.4%.

Claims 10 and 22 are vague in reciting "lower". The term "lower" is a relative one not defined by the claim, no single set of conditions is recognized by the art as being "lower" and because the specification does not provide a standard for ascertaining the requisite degree, the metes and bounds of this claim cannot be established.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-12 and 14-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for temperature regulated promoters selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:2, wherein the promoters are operably linked to *cdc-18,* β-galactosidose, streptokinase or GFP and vectors desposited as MTCC 5106 and 5107 wherein *S. pombe* cells transformed with plasmids comprising *nmt-146* and *nmt-185* after 3 hours of induction have enhanced expression of *cdc18* and wherein when *S. pombe* cells are transformed with pREP3x expressing β-galactosidose under control of *nmt-185*, β–gal is expressed at levels of 124 units and wherein when *S. pombe* cells are transformed with pJRK2 expressing streptokinase under control of *nmt-*

185 SK is expressed at 870 I.U.mg protein and expressing GFP under control of *nmt-185* in which 91.4% of cells express GFP wherein induction comprises transfer of cells to 25°C in the absence of thiamine, does not reasonably provide enablement for any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

The instant claims are drawn to promoters and vectors comprising the promoter wherein the promoters are *nmt-146* and *nmt-185*, SEQ ID NO:2 and 1 comprising 185 and 146 nucleotide fragments of a previously isolated promoter *nmt-1*. Furthermore, the claims are drawn to promoters and vectors with expression capabilities of GFP of 95% and 91.4%, β-galactosidase of 124.3+/- 20 units and 150 +/- 20 units and with maximum specific activity of 900 I.U/mg an 870+/- I.U/mg. As well, the promoters enhance *cdc18*, give leaky lower expression and are not deleterious to the cell viability and reduce the level of proteolytic degradation.

The specification teaches that genomic DNA was partially digested with SauI and clones were isolated. Two such clones exhibited enhanced expression of GFP at 25°C and

no expression at 36°C. While the sequences are fragments of the *S. pombe* promoter *nmt-1*, pGFP plasmids containing nmt-185, nmt-146 or nmt1 promoters in S. pombe were assayed for GFP expression. "It was observed that nmt1, nmt-146 and nmt-185 promoters were repressed in presence of thiamine at 36°C as monitored by green fluorescence. However, in absence of thiamine at 36°C, while nmt1 promoter was derepressed, i.e., GFP gave green fluorescence, the nmt-185 and nmt-146 promoter remained repressed, i.e., GFP gene gave no green fluorescence. On the other hand at 25 ° C, *nmt1, nmt-185 and nmt-146* were expressed as indicated by green fluorescence when grown in absence of thiamine. But in presence of thiamine all three promoters were again repressed. Thus, the nmt-185 and nmt-146 promoters can be regulated by a temperature shift: they are repressed at 36°C, but expressed upon shift to 25°C in absence of thiamine. In contrast, the *nmt1* promoter is equally expressed at 36°C and 25°C in absence of thiamine." Specifically, applicants demonstrate that *S. pombe* cells transformed with plasmids comprising *nmt-146* and *nmt-185* can drive expression of *cdc18* (example 3). pREP3X-lacZ expressing lacZ under control of *nmt-185* exhibited maximal expression of β-gal at 3 hours in which the level was 124.3+/-20 units (table 3) and with *nmt-146* but no specific levels are described. In *S. pombe* cells transformed with pJRK2 expressing streptokinase, maximum levels of specific activity of SK was detected at 870 I.U.mg protein after 3 hours of induction and with *nmt-146* the specification teaches that levels were similar. Table 5 states that 91.4% of cells express GFP after 3 hours of induction.

Promoter sequences (claims 1-12) are drawn to expression capabilities of GFP, β-galactosidase and *cdc-18* by the instant promoters within 3 hours. However, the promoter as recited does not include explicitly recite operable linkage to the recited

genes. As well, the promoters express the proteins within three hours of induction. Induction comprises transfer of cells to 25°C in the absence of thiamine when the promoters comprising the operably linked genes are introduced into *S. pombe* cells. It is highly unpredictable that in the absence of operably linkage of coding sequences for GFP, β-galactosidase and *cdc-18* to the promoters, cells comprising the sequences and induction conditions that the recited expression levels would be possible as the promoters themselves are not absent the cells and vector components such as coding sequences capable of expressing the recited proteins.

Claims 13-24 are drawn to vectors comprising the *nmt-186* and *nmt-146* sequences. The vectors are deposited under Accession number MTCC 5106 and 5107 respectively and are depicted in figures 2 and 3 as pJRK2 or pJRK3. Both sets of claims are drawn to specific activity with expression capabilities of GFP of 95% and 91.4%, β-galactosidase of 124.3+/- 20 units and 150 +/- 20 units and with maximum specific activity of 900 I.U/mg an 870+/- I.U/mg. The specification teaches, *S. pombe* cells transformed with plasmids comprising *nmt-146* and *nmt-185* can drive expression of *cdc18*, *S. pombe* cells transformed with pREP3x express β-galactosidose under control of *nmt-185* express β-gal at levels of 124 units and *S. pombe* cells transformed with pJRK2 expressing streptokinase under control of *nmt-185* express SK at levels of 870 I.U.mg protein and 91.4% of cells express GFP after 3 hours of induction wherein induction comprises transfer of cells to 25C in the absence of thiamine. Furthermore, the experimental evidence of expression levels is present for *nmt-185* under particular conditions but not for *nmt-146*.

As an initial issue, the vectors do not comprise components required of the vectors of claims 15-21. Specifically, the deposited vectors do not have the capability of expression of GFP, β-galactosidase and *cdc-18* because they are not present in the vectors. As well, in claims 14, 16, 20 and 22-24, the claims describe functional limitations that are inherently present in either pRJK2 (claim 14, 16, 20, 22-24) or pRKJ3 (claim 14 and 22-24). Because there are no additional structural requirements of the vector based upon the functional properties, the claims do not further limit claim 13. Hence, functional limitations used to further define the vectors in dependent claims 14-24 cannot actually define the claims as they are not accompanied by distinct structural components that perform the functions. However, should claims 15-20 be amended to incorporate limitations directed to the coding sequences, the specification does not disclose the activity of all of the resulting vectors. For example, neither vector was shown to be used to express β-galactosidase. Rather, pREP3xlacZ comprising the promoters and coding sequences was used for these studies, which is not encompassed by the claims. In addition expression of GFP as well as maximum specific activity was not demonstrated for pRJK3 and so it cannot be known if those values were attained. The court and the Board have repeatedly held (Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,18 USPQ2d 1016 (CA FC, 1991); Fiers v. Revel, 25 USPQ2d 1601 (CA FC 1993); Fiddes v. Baird, 30 USPQ2d 1481 (BPAI 1993) and Regents of the Univ. Calif. v. Eli Lilly & Co., 43 USPQ2d 1398 (CA FC, 1997)) that an adequate written description of a nucleic acid requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it, irrespective of the complexity or simplicity of the method; what is required is a description of the nucleic acid itself. In

this case, specific activity of the promoter is recited however the ability of the vectors and promoters to reach the specifically recited activity is not shown. Factors such as cell types, other components in pREP3XlacZ that were used in the studies may affect the levels of expression in ways that cannot be transposed to the disclosed vectors. In effect, applicants have not disclosed the recited vectors.

The MPEP teaches, "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b). In the instant case, the claims lack critical elements to provide the recited function and given the lack of guidance and disclosure in the specification undue experimentation would be required to identify the proper configurations to provide the exact expression levels.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 10, 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Parker et al (WO 94/03609).

Transitional phrases such as "having" must be interpreted in light of the specification to determine whether open or closed claim language is intended. See, e.g., Lampi Corp. v.American Power Products Inc., 228 F.3d 1365, 1376, 56 USPQ2d 1445, 1453 (Fed. Cir. 2000). In the instant case, applicants disclose *nmt-1* and as such this promoter comprises SEQ ID NO:1 and 2 lending the term an "open" configuration.

Parker et al teach a promoter having SEQ ID NO:1 (see e.g. SEQ ID NO:3). Lower leaky expression of protein is provided such as lower then CMV or SV40 or other commonly used promoters as nmt-1 is repressed in the presence of thiamine. The promoter is not deleterious to cell viability as demonstrated by the ability to use it in *S. pombe* cells (see e.g. figure 7).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Maria B Marvich, PhD
Examiner
Art Unit 1633